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I, Melissa Stanford, a translator with Chillson Translating Service, 3530 Chas Drive, Hampstead, Maryland, 21074, hereby declare as follows:

That I am familiar with the German and English languages;

That I am capable of translating from German to English;

That the translation attached hereto is a true and accurate translation of German Application 100 27 170.7, filed May 31, 2000, titled, "Human PEM as a Target for Birth Control;"

That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true;

And further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any registration resulting therefrom.

By Melissa Stanford

Executed this 10 day of Jan 2004.

Witness Anne Chillson

FEDERAL REPUBLIC OF GERMANY

Priority Certificate on the Filing of a Patent Application

File Number:	100 27 170.7
Date of Application:	May 31, 2000
Applicant/Holder:	Schering Aktiengesellschaft, Berlin/DE
Title:	Human PEM as a Target for Birth Control
IPC:	C 12 Q, C 12 N and A 61 K

The attached copies are a true and accurate rendition of the original documents of this patent application.

Munich, May 16, 2001

The German Patent and Trademark Office

The Director

/s/

Weihmayr

Human PEM as a Target for Birth Control

Description

The invention relates to the human PEM polypeptide, which plays an important role for the maturation of sperm and the nucleic acid that codes for them. The invention comprises the use of PEM as a target in male birth control and for the treatment and diagnosis of male infertility. The invention also includes a selection process for PEM antagonists as well as the production of binding molecules, which specifically detect PEM. In addition, genes that are regulated by the PEM gene are part of this invention.

The intention to use proteins of the male reproductive tract or sperm proteins as a target group for non-hormonal contraception has been known for several decades. For example, a project with the name "Vaccines for Fertility Regulation" was supported by the World Health Organization (WHO) (P. D. Griffin, Hum. Reprod., 1991, 6: 166-172). Various sperm proteins such as, e.g., PH-20, SP-10, FA-1, FA-2, CS-1, NZ-1, NZ-2 and lactate-dehydrogenase C4 were proposed as candidates for immunocontraception (R. K. Naz, Immunol. Rev., 1999, 171: 193-202). Immunization tests with PH-20 showed that both male and female animals are thus completely and reversibly infertile (P. Primakoff et al., Nature, 1988, 335: 543-546). The use of the intra-acrosomal sperm protein SP-10 as an antigen caused an immunological response in women that reduces fertility (R. W. Wright et al., Biol. Reprod., 1990, 42: 693-701). Active immunization of animals with FA-1 produces a lasting and reversible inhibition of fertility (R. K. Naz and X. Zhu, Biol. Reprod., 1998, 59: 1095-1100).

PEM is a transcription factor that includes the Homeobox family. The corresponding cDNA was cloned from the mouse (M. F. Wilkinson et al., Dev. Biol., 1990, 141: 451-455) and from the rat (S. Maiti et al., J. Biol. Chem., 1996, 271: 17536-17546). PEM transcripts are expressed abundantly and selectively in the male genital tract. In the mouse, the PEM expression was mainly detected in the testes, while in the rat, PEM can mainly be found in the

epididymis (K. A. Sutton et al., J. Androl., 1998, 19: 21-30). The in vivo expression of the PEM gene is regulated in these organs by androgens. In addition, PEM transcripts were described in the muscle and in macrophages, but in these cases, the PEM expression does not seem to be regulated by androgens, which can be attributed to the use of different promoters (S. Maiti et al., J. Biol. Chem., 1996, 271: 17536-17546). Despite the unremarkable phenotype of the PEM-knock-out mouse (J. L. Pitman et al., Dev. Biol., 1998, 202: 196-214), it can be assumed that the human PEM plays an essential role in spermatogenesis and/or in sperm maturation. PEM is the sole known transcription factor whose expression is regulated by androgens (S. Maiti et al., J. Biol. Chem., 1996, 271: 17536-17546).

No one has yet found the human PEM ortholog; this suggests a low sequence conservation in different organisms, as can already be determined by the weak identity (73%) between mouse PEM and rat PEM (S. Maiti et al., Genomics, 1996, 34: 304-316).

The invention relates to the identification of human PEM by examination of public DNA data bases. Both the complete coding PEM-cDNA sequence and the structure of the PEM gene could be determined. The inhibition of PEM can result in the inhibition of sperm development or maturation and thus represents a novel approach for contraceptive preparations. In addition, the screening for functional mutations in the PEM gene can be used as a diagnostic agent for determining the causes of infertility. By restoring PEM function (e.g., by gene therapy), patient fertility can also be restored.

A subject of the invention is thus the use of human PEM or a nucleic acid that codes for this as a target substance for the production of an agent for birth control. The human PEM is preferably coded by (a) the coding area of the nucleic acid sequence shown in SEQ ID No. 1, (b) one of the sequences according to (a) against the backdrop of the degeneration of the genetic code and/or (c) one of the nucleic acid sequences that hybridize under stringent conditions with the sequences according to (a) and/or (b). The human PEM especially preferably has the amino acid sequence shown in SEQ ID No. 2 or an amino acid sequence that is at least 80%, preferably at least 90%, identical to it.

The term "stringent hybridization" according to this invention is used in this case as in Sambrook et al. (Molecular Cloning, A Laboratory Manual, Cold Spring Harbor, Laboratory Press (1989), 1.101-1.104). Accordingly, we speak of hybridization under stringent conditions, if after washing for one hour with 1 x SSC and 0.1% SDS at 55°C, preferably at 62°C and especially preferably at 68°C, especially for one hour with 0.2 X SSC and 0.1% SDS at 55°C, preferably at 62°C and especially preferably at 68°C, a positive hybridization signal is still observed. A sequence that hybridizes under such washing conditions with a nucleotide sequence that is shown in SEQ ID No. 1 or a nucleotide sequence that thus corresponds against the backdrop of the degeneration of the genetic code is detected by this invention.

In particular, this invention detects natural, allelic variations of PEM, in which these are optionally also functional mutations. Moreover, recombinant variants, for example functional partial fragments (such as, for example, the "Divergent Paired Class" homeodomains as described for the mouse of Rayle (Develop. Biol. 146 (1991), 255-257)), are also detected by this invention.

Especially preferably, the human PEM exhibits the amino acid sequence that is shown in SEQ ID No. 2 or a sequence that is at least 80%, and especially at least 90%, identical to it. The 1% identity is in this case calculated according to the following formula:

$$I = n/L \times 100\%,$$

whereby n stands for the number of identical amino acids of the two sequences that are compared to one another and L stands for the length of the sequence section used for comparison.

An inhibition of human PEM can be used for inhibiting fertility and especially for inhibiting spermatogenesis in male mammals. This is of great importance in human contraception, but also in veterinary medicine for population control. The inhibition of PEM can be carried out by expression reduction by means of antisense-nucleic acids or ribozymes or on the protein level by using inhibitors such as anti-PEM-antibodies or low-molecular antagonists. The production of antisense molecules and ribozymes can be carried out, for

example, as described in Sczakiel (Antisense Nucleic Acid Drug Dev. 7 (1997), 439-444, Lavrovsky et al. (Biochem. Mol. Med. 62 (1997), 11-22) and Thompson (Methods Enzymol. 306 (1999), 241-260). Polyclonal antibodies against human PEM can be carried out by immunization of test animals with human PEM or fragments thereof, optionally on a vehicle such as keyhole-limpet-hemocyanin, and recovery of the resulting antibodies from the immunized test animal. Monoclonal antibodies can be obtained by, for example, fusion of spleen cells of the immunized test animal with myeloma cells according to the method of Köhler and Milstein or further developments thereof. Low-molecular inhibitors of PEM can be identified by a screening process as explained in more detail below.

By contrast, an activation of human PEM to increase fertility can be used. Also here, applications both in human medicine and in veterinary medicine are possible. The activation of PEM can be carried out by, for example, increasing the PEM expression in target cells, e.g., Sertoli cells in the testes and/or epithelial cells in the epididymis, by means of gene-therapy methods. To this end, a nucleic acid that codes for PEM can be introduced into the target cell under the control of an active promoter in the target cell by means of suitable gene transfer vectors, e.g., viral vectors such as, for example, adenoviruses, retroviruses, adeno-associated viruses or vaccinia viruses, or plasmids, and can be expressed there. Suitable gene therapy processes are described in, e.g., Gomez-Navarro et al. (Eur. J. Cancer, 35 (1999), 867-885). In addition, an activation of PEM can be carried out by low-molecular active substances, which can be identified by a screening process as described below.

Another subject of the invention is a process for the preparation of new agents for birth control. The identification of these new agents is carried out in that the ability of test substances to modulate human PEM is determined. This determination can be performed as a high-throughput test, in which a considerable number of test substances are studied in parallel. The test can be performed on a cellular basis, whereby cells can be used that are transfixed with the gene for the human PEM and are able to produce an over-expression of this gene. In contrast, cells can also be tested that contain a completely or partially defective PEM, for example cells

that contain a defective human PEM gene in at least one allele, preferably in both alleles. The test cells that are used for the identification of new active substances are preferably mammal cells, especially human cells. As an alternative, a test on a molecular basis can be performed, whereby the human PEM is used in the form of cell extracts or in an essentially isolated and purified form, optionally also in the form of an active fragment.

In addition, the process according to the invention for identifying new agents for birth control can comprise the formulation of test substances that exert a modulatory action on human PEM, or compounds derived therefrom, into a pharmaceutical agent.

Still another subject of the invention is a diagnostic process in which the expression and/or the functionality of human PEM is determined in a sample. The sample preferably originates from a patient who is to be subjected to a fertility determination. The determination of PEM can be carried out on the nucleic-acid level, e.g., on the DNA level, for example by Southern Blot or determination of single nucleotide polymorphisms, on the transcript level by determination of the degree of expression, the expression pattern or the transcript length, or on the protein level, e.g., by immunohistochemical or immunocytochemical methods or by function measurements. The determination of single-nucleotide-polymorphisms allows the identification and diagnosis of functional mutations, which may be the cause of infertility in patients.

Another subject of the invention is a cell that is transfixed with a DNA that codes for the human PEM or a fragment thereof and that contains at least one exogenic copy of this DNA. Still another subject of the invention is a cell that contains a defective PEM gene in at least one allele, for example a PEM gene that is disrupted by means of homologous recombination. These cells can be used just like the nucleic acids, which code for human PEM or a fragment thereof, or the human PEM protein itself or a fragment thereof for identifying and characterizing agents for birth control.

Finally, the invention relates to a process for identifying genes that are regulated by the human PEM gene, whereby the influence of human PEM on the gene expression in human cells is tested. This test can be carried out by, for example, transcriptome analysis, e.g., according to

the methods described by Kozian and Kirschbaum (Trends Biotechnol. 17 (1999), 73-78) or by proteome analysis according to the methods described by Dutt and Lee (Curr. Opin. Biotechnol. 11 (2000), 176-179). The genes that are identified by the process and their use as a target substance for the production of an agent for birth control are also subjects of this invention.

In addition, the invention is to be explained by the figures below.

Here:

SEQ ID No. 1 shows the nucleotide sequence of a strand of human PEM cDNA (the sequence of the complementary strand is also a component of SEQ ID No. 1)

SEQ ID No. 2 shows the amino acid sequence of human PEM

SEQ ID No. 3 shows the genomic human PEM sequence.

Starting from the murine PEM sequence (Wilkinson et al., (1990), supra), the human EST clones and human genomic clones were found that are highly homologous enough to be considered PEM orthologs. The human genomic locus could be defined in Xq 25-26.

The cDNA sequence that is identified in EST data bases is shown in SEQ ID No. 1, and the protein-coding sequence is shown in SEQ ID No. 2. The genomic sequence could also be identified in this way and is shown in SEQ ID No. 3 (corresponding to a cross-section of nucleotides 16000-170967 from Gene Bank Accession No. AC005023). The initial exon extends from nucleotide 168 439 to 168 042. An internal exon extends from nucleotide 165 491 to 165 446, and the terminal exon extends from nucleotide 161 927 to 161 817 (111 nucleotides). In the range of nucleotides 161 698 to 161 693, there is a polyadenylating signal.

Claims

1. Use of human PEM or a nucleic acid that codes for this as a target substance for the production of an agent for birth control.
2. Use according to claim 1, characterized in that the human PEM is coded by (a) the coding area of the nucleic acid sequence that is shown in SEQ ID No. 1, (b) one of the sequences according to (a) against the backdrop of the degeneration of the genetic code and/or (c) a nucleic acid sequence that hybridizes under stringent conditions with the sequences according to (a) and/or (b).
3. Use according to claim 1 or 2, wherein the human PEM has the amino acid sequence that is shown in SEQ ID No. 2 or an amino acid sequence that is at least 80% identical to the amino acid sequence.
4. Use according to one of claims 1-3, wherein an inhibition of PEM is used to reduce fertility.
5. Use according to one of claims 1-3, wherein an activation of PEM is used to increase fertility.
6. Process for identifying agents for birth control, wherein the ability of test substances to modulate PEM is determined.
7. Use according to claim 6, wherein a high-throughput test is performed.
8. Process according to claim 6 or 7, wherein a test is performed on a cellular basis.
9. Process according to claim 6 or 7, wherein a test is performed on a molecular basis.
10. Process according to one of claims 6-9, in addition comprising the formulation of the test substances that have a modulatory action or compounds derived therefrom into a pharmaceutical agent.
11. Process for fertility diagnosis, wherein the expression and/or functionality of human PEM is determined in a sample.
12. Cell, wherein it is transfixed with a nucleic acid that codes for human PEM or a

fragment thereof.

13. Human cell, wherein it contains a defective PEM gene in at least one allele.
14. Process for identifying genes that are regulated by the human PEM gene, wherein the effect of human PEM on the gene expression in human cells is tested.
15. Process according to claim 14, wherein a transcriptor analysis or proteome analysis is performed.

Abstract

The invention relates to the human PEM polypeptide that plays an important role for the maturation of sperm, and the nucleic acid that codes for them. The invention comprises the use of PEM as a target in male birth control and for the treatment and diagnosis of male infertility. The invention also includes a selection process for PEM antagonists as well as the production of binding molecules, which specifically detect PEM. In addition, genes that are regulated by the PEM gene are part of this invention.

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151  CCTCATGGGT AATATGAACC CTGAGGGCGG TGTGAACCAC GAGAACGGCA
201  TGAACCGCGA TGGCGGCATG ATCCCCGAGG GCGGCGGTGG AAACCAGGAG
251  CCTCGGCAGC AGCCGCAGCC CCCGCCGGAG GAGCCGGCCC AGGCGGCCAT
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351  TCACGCTGTT GCAGGTGGAG GAGCTGGAAA GTGTTTTCCG ACACACTCAA
401  TACCCTGATG TGCCCACAAG AAGGGAACTT GCCGAAAACT TAGGTGTGAC
451  TGAAGACAAA GTGCGGGTTT GGTTTAAGAA TAAAAGGGCC AGATGTAGGC
501  GACATCAGAG AGAATTAATG CTCGCCAATG AACTACGTGC TGACCCAGAC
551  GACTGTGTCT ACATCGTCGT GGACTAG
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SEQ ID No. 2

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MQPRTRRTKF TLLQVEELES VFRHTQYPDV PTRRELAENL GVTEDKVRVW

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SEQ ID No. 3

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